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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,628	11/15/2001	David Botstein	P2730P1C30	7410

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	PAPER NUMBER
1647	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/997,628	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	SANDRA WEGERT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/30/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims

The amendment and the Remarks/Arguments submitted 30 September 2008 have been received and considered. Claims 1-118 and 124 are canceled. Claim 119 is amended. Claims 119-123 are under examination.

Maintained Objections and/or Rejections

35 U.S.C. §§ 101 and 112, First Paragraph - Utility, Enablement

35 U.S.C. 101 reads as follows:

> **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 119-123 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

Claims 119-123 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific,

and substantial asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

In the interest of clarity, the basis of the maintained rejections is set forth here:

The claims are directed to antibodies that specifically bind the polypeptide of SEQ ID NO: 349. Dependent claims are directed to monoclonal and humanized antibodies, antibody fragments, and antibodies which have been labeled.

Applicants have gone on the record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides. See Remarks/ Arguments (received 30 September 2008) at p. 4.

At pages 539-555 of the specification, Example 170 discloses a gene amplification assay in which genomic DNA encoding PRO1097 had a ΔCt value of at least 1.0 for two out of 14 lung tumors and three out of 14 colon tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 170 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 539, lines 21-24) and the claimed cognate antibody may therefore be used to detect the PRO1097 polypeptide. At page 548, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA

results." It is noted that at page 548 it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 550-554 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29).

As discussed in the previous Office Action (30 April 2008, p. 4-5) there are several problems with the data provided in Example 170 of the instant Specification. For example, the art recognizes that lung and colon epithelium can be aneuploid even when it is not cancerous (see Hittelman, et al, 2001, Ann. N. Y. Acad. Sci. 952:1-12, esp. p. 4, of record; Fleischhacker et al., 1995, Modern Pathology 8:360-365, especially p. 360, 1st paragraph of introduction). The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium and does not correct for aneuploidy. Thus it is not clear that PRO1097 is amplified in cancerous colon epithelium or lung tissue more than in damaged (non-cancerous) colon epithelium or lung tissue. One skilled in the art would not conclude that PRO1097 is a diagnostic probe for cancer unless it is clear that PRO1097 is amplified to a clearly greater extent in true tumor tissue relative to non-cancerous tissue of the same origin. These problems with the data are also magnified by the fact that only a *minority* of tumor samples demonstrated gene amplification, according to Example 170 of the Specification. For example, only five tissue samples of the 34 tumors measured were reported to have elevated gene levels (see Table 9B).

In addition, even if the data had been corrected for aneuploidy and a proper control had been used, the data have no bearing on the utility of the PRO1097 polypeptides or the claimed cognate antibodies made against the polypeptides. In order for the PRO1097 polypeptide to be overexpressed in tumors, amplified genomic DNA

would have to correlate with increased polypeptide levels. As discussed in the last Office Action (30 April 2008, pp. 9-11) and contrary to Applicants' arguments (Remarks, 30 September 2008, p. 10, for example) no data regarding PRO1097 polypeptide levels in lung or colon tumors have been brought forth on the record. And, as discussed in the previous Office Action (30 April 2008, p. 5), a positive correlation between genomic DNA levels and polypeptide levels cannot be presumed (Pennica et al., 1998, PNAS USA 95:14717-14722, of record).

Applicants maintain that "in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level" (Remarks, pp. 4, 7, 8 and 17), and cite the Goddard Declaration (submitted under 37 § CFR 1.132, submitted 22 August 2005) and Pennica et al (of record) as support. However, as discussed in previous Office actions (30 April 2008 and 30 March 2007) the Goddard Declaration discusses the accuracy of the Taq DNA polymerase assay, and cites several references that attest to the use of the assay in diagnosing and prognosticating disease. Such a discussion evinces that the instant application provides a mere invitation to experiment, and not a readily available utility. In fact the accuracy of the gene amplification assay is not in doubt, only that gene amplification does not suggest a function for the claimed antibodies, nor for the PRO1097 gene or gene products. Furthermore, the fact that it may be "more likely than not" that gene amplification is associated with expression of the gene product-which the examiner does not agree with-does not predict what the *specific* result would be for the gene product of PRO1097.

Applicants also discuss the references submitted in the instant application, such as Orntoft et al, Hyman, et al and Pollack et al, that demonstrate that "in general, there is a

correlation between mRNA levels and polypeptide levels" (Remarks, p. 5). Applicant's arguments have been fully considered but they are not persuasive for the following reasons: As discussed in the previous Office actions (30 march 2007 and 30 April 2008), the Specification only discloses measuring PRO1097 DNA in samples of colon or lung tumors. There is no measurement of corresponding mRNA or protein levels. Therefore, the arguments pertaining to the usefulness of mRNA and polypeptide levels simply have no bearing on the utility of the claimed PRO1097 antibodies. Furthermore, all three references were published in 2002, well after the priority date. Utility is determined as of the filing date. *In re Brana*, 51 F.3d at 1567. It is noted that Godbout et al., Hanna and Mornin, and Pennica et al., all of which support the rejection, were each published close to the priority date of the instant application.

Applicants also discuss the usefulness of the gene amplification assay to enable "more accurate tumor classification" (Remarks, p. 5) or to diagnose "pre-cancerous lesions" or to assay tissues for "cancer risk" (Remarks, p. 6) and cite the Ashkenazi Declaration (filed 10 September 2004). Applicant's arguments have been fully considered but are not persuasive for the following reasons: Such uses for PRO1097 are not specific, but can be said to be true for many other gene products besides PRO1097. In other words, expression levels of any gene product in cancerous tissue would be informative, but does not represent a *specific* use for PRO1097. In addition, the Ashkenazi Declaration itself appears to express uncertainty about a specific and substantial utility for PRO1097, stating "if gene amplification results in over-expression" and "even in the absence of over-expression of the gene product, amplification of a cancer marker gene [ ] is useful in the diagnosis or classification of cancer," thus acknowledging that there may

not be increased expression of gene product associated with PRO1097 after all (Declaration, 10 September 2004, paragraphs 5-6). The Ashkenazi declaration also acknowledges that "An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy" (paragraph 5) thereby confirming arguments made above by the examiner concerning aneuploidy in colon and lung epithelial tissue. It is also important to note that the specification never asserts a utility for PRO1097 involving tumor classification or diagnosis of pre-cancerous lesions or cancer risk. Thus, the Ashkenazi declaration and Applicant's arguments contradict the assertion of utility in the specification, which is that PRO1097 is diagnostic for cancer alone.

Applicants also discuss the validity of the pooled blood controls used in the present application (Remarks, p. 8, referring to the Office action of 30 April 2008, p. 8). Applicants argue that Bieche et al. (of record) used normal leukocyte DNA derived from a small subset of breast cancer patients and note that the results of the study are consistent with those reported in the literature. Applicants conclude from this study and that in Pennica, et al and Pitti, et al (of record) that the art demonstrates that pooled normal blood samples are considered to be valid negative controls for gene amplification experiments.

Applicants' arguments have been fully considered but are not found to be persuasive. Specifically, although Pennica et al. and Pitti et al. compare gene amplification of specific genes in colon and lung tumors to pooled DNA from 10 healthy normal donors, Pennica et al. and Pitti et al. are not attempting to utilize the data generated from the experiments for diagnostic purposes (as is Example 170 of the instant

application). Secondly, Bieche et al. is simply utilizing real-time PCR to validate an assay for the detection and determination of the copy numbers of the three most frequently amplified genes in breast tumors (*myc, ccnd1*, and *erbB2*). That research group compared the results for 108 breast tumors with previous Southern-blot data for the same samples (abstract; p. 662, column 1). The genes studied by Bieche et al. were already well-known in the art to be amplified in breast cancer. Thus, in that case it was not necessary to utilize matched normal tissue samples. Furthermore, each of Pennica et al., Pitti et al., and Bieche et al. did not rely solely upon the PCR assay using a control from blood genomic DNA to make conclusions. Pennica et al. also used controls from normal mucosa, surgical specimens, and several cell lines (p. 14718, left column). Pitti et al. also looked at northern blot analysis, ligand binding analysis, apoptosis induction analysis, and in situ hybridization analysis. Pitti et al. also ran an additional control in the PCR assays, using flanking DNA regions in tumor samples compared to blood DNA samples (p. 701, paragraph bridging the two columns). Bieche et al. relied upon Southern blotting to confirm the PCR results and note that not all samples showing PCR amplification also showed amplification by Southern blotting (p. 664, last paragraph before Discussion section). This was especially true for sequences that were amplified at low levels comparable to the levels that instant PRO1097 was shown to be amplified. Applicants also discuss the Konopka et al, Godbout et al, Li et al, and Hanna and Mornin references (Remarks, pp. 12-13) as pertaining to the argument of whether or not mRNA levels are predictive of protein levels. As explained in the previous Office action (30 April 2008), the examiner is no longer arguing this point. As to the relationship between gene amplification and overexpression, which is relevant to a utility for

PRO1097, the Ashkenazi Declaration of 10 September 2004 appears to support the concept that gene amplification is not always predictive of overexpression, thus supporting the examiner's position and contradicting the assertions in the specification that gene amplification indicates overexpression without indicating the possibility of exceptions. Furthermore, the Konopka et al., Godbout et al., Li et al., and Hanna and Mornin references support the rejection in that they show that gene amplification does not correlate with mRNA or protein overexpression.

Data pertaining to PRO1097 genomic DNA do not indicate anything significant regarding the claimed PRO1097 antibodies. The data do not support the specification's assertion that antibodies raised against PRO1097 can be used as cancer diagnostic agents, or to support the Ashkenazi declaration and applicant's asserted utility that antibodies raised against PRO1097 can be used to classify tumors, or to diagnose pre-cancerous lesions. Significant further research would have been required of the skilled artisan to reasonably confirm that the disclosed PRO1097 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents; thus the asserted utility is not substantial. In addition, not all samples of tumor tissue showed amplification of the PRO1097 gene, thus making it, statistically speaking, a very poor predictor of any cancerous or pre-cancerous condition in samples of unknown tissue. In addition, in the absence of information regarding whether or not PRO1097 polypeptide levels are also different between specific cancerous and normal tissues (such that detection would be a useful function), the proposed use of the PRO1097 polypeptides as therapeutic targets of the claimed antibodies, is simply a starting point for further research and investigation into potential practical uses of PRO1097 (See Brenner v.

Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966)).

In view of the preponderance of evidence supporting the rejections, the rejections are properly maintained.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

US 20030152999 (Ashkenazi et al.). It is noted that a recent Board decision in this commonly assigned case affirmed the utility and enablement rejections based on a fact pattern that is nearly identical to the one in the instant application.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Manjunath Rao, can be reached at (571) 272-0939.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO

Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

SLW

6 January 2009

/Elizabeth C. Kemmerer/

Elizabeth C. Kemmerer, Ph.D.

Primary Examiner, Art Unit 1646